Appl. No. 10/621,966 Amendment dated February 2, 2007 Office Action dated December 15, 2006

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

1. (Previously presented) A method of modulating an endothelial gene differentiation-1 ("Edg-1") receptor mediated for vasoconstriction, comprising contacting a cell expressing the Edg-1 receptor with an amount of a non-phospholipid modulator of the Edg-1 receptor sufficient to modulate the Edg-1 receptor mediated for vasoconstriction, wherein said modulator is a compound of Formula (Ia):

$$R^{5}$$
 R^{5}
 R^{2}
 R^{3}
 R^{1}
 R^{1}

or a pharmaceutically acceptable solvate or hydrate thereof, wherein

n is a member selected from the integers 0 to 5;

R¹ is a member selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylamino, substituted alkylamino, alkylamino, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylalkyl, arylamino, substituted arylamino, cycloalkyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, and substituted heteroalkyl; each R², R³ and R⁵ is a member independently selected from the group consisting of

hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted

22

23

24

25

26

27

28

29

30

31

32

3334

35

36

37

38

39

40

1

2

3

4

acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro and thio; and each R⁴ is a member independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro and thio.

2. (Previously presented) A method of modulating an Edg-1 receptor mediated for vasoconstriction in a subject, comprising administering to the subject a therapeutically effective amount of a non-phospholipid modulator of the Edg-1 receptor, wherein said modulator is a compound of Formula (Ia):

$$(R^4)_n$$

$$R^5$$

$$R^3$$

$$R^1$$

$$(Ia)$$

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

2.7

28

or a pharmaceutically acceptable solvate or hydrate thereof, wherein:

n is a member selected from the integers 0 to 5;

R¹ is a member selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, and substituted heteroalkyl; each R², R³ and R⁵ is a member independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio,

alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro and thio; and

29	each R ⁴ is a member independently selected from the group consisting of hydrogen, halo,
30	alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino,
31	alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy,
32	substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino,
33	substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl,
34	substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted
35	arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano,
36	cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl,
37	dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted
38	heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted
39	heteroalkyl, hydroxyl, nitro and thio.

- 1 3. (Canceled)
- 1 4. (Canceled)
- 1 5. (Canceled)
- 1 **6.** (Canceled)
- 1 7. (Canceled)
- 1 **8.** (Canceled)
- 1 **9.** (Canceled)
- 1 **10.** (Canceled)
- 1 **11.** (Canceled)
- 1 **12.** (Canceled)
- 1 **13.** (Canceled)

Appl. No. 10/621,966 Amendment dated February 2, 2007 Office Action dated December 15, 2006

PATENT

1	14.	(Canceled)
1	14.	(Canceled)

- **15.** (Canceled)
- **16.** (Canceled)
- **17.** (Canceled)
- **18.** (Canceled)
- **19.** (Canceled)
- **20.** (Canceled)
- **21.** (Canceled)
- **22.** (Canceled)
- **23.** (Canceled)
- **24.** (Canceled)
- **25.** (Canceled)
- **26.** (Canceled)
- **27.** (Canceled)
- **28.** (Canceled)
- **29.** (Canceled)
- **30.** (Canceled)
- **31.** (Canceled)

- **32.** (Canceled)
- **33.** (Canceled)

1 34. (Previously presented) A method for treating vasoconstriction in cerebral arteries in a
2 subject in need of such treatment, said method comprising administering to said subject a
3 therapeutically effective amount of a compound of Formula (Ia), wherein said compound
4 of Formula (Ia) is:

$$(R^4)_n$$
 R^5
 R^3
 R^1
 (Ia)

or a pharmaceutically acceptable solvate or hydrate thereof, wherein

n is a member selected from the integers 0 to 5;

R¹ is a member selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylamino, alkylamino, alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, and substituted heteroalkyl;

each R², R³ and R⁵ is a member independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylamino,

substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted 22 alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, 23 substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted 24 arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted 25 arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, 26 substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, 27 28 dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted 29 heteroalkyl, hydroxyl, nitro and thio; and 30 each R⁴ is a member independently selected from the group consisting of hydrogen, halo, 31 alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, 32 alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, 33 substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, 34 substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, 35 substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted 36 arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano, 37 cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, 38 dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted 39 heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted 40 heteroalkyl, hydroxyl, nitro and thio. 41 (Previously presented) A method for treating vasoconstriction in a subject in need of such 1 35. treatment, said method comprising administering to said subject a therapeutically 2 effective amount of a compound of Formula (Ia), wherein said compound of Formula (Ia) 3

is:

$$R^{5}$$
 R^{5}
 R^{2}
 R^{3}
 R^{3}
 R^{4}
 R^{5}
 R^{2}

or a pharmaceutically acceptable solvate or hydrate thereof, wherein

n is a member selected from the integers 0 to 5;

R¹ is a member selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylamino, alkylamino, alkylamino, alkylamino, alkylamino, alkylamino, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, and substituted heteroalkyl;

each R², R³ and R⁵ is a member independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted

heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted 29 heteroalkyl, hydroxyl, nitro and thio; 30 each R⁴ is a member independently selected from the group consisting of hydrogen, halo, 31 alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, 32 alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, 33 substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, 34 substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, 35 substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted 36 arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano, 37 cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, 38 dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted 39 heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted 40 41 heteroalkyl, hydroxyl, nitro and thio; and one or more antagonists of an Edg receptor. 42

1 **36.** (Previously presented) A method for treating in a subject in need of such treatment, said method comprising administering to said subject a therapeutically effective amount of a compound of Formula (Ia), wherein said compound of Formula (Ia) is:

$$\begin{array}{c|c}
(R^4)_n & R^5 & R^2 \\
\hline
 & N & N & R^1
\end{array}$$
(Ia)

or a pharmaceutically acceptable solvate or hydrate thereof, wherein

n is a member selected from the integers 0 to 5;

R¹ is a member selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylamino, substituted alkylamino, a

4

5

6

7

8

10	alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino,
11	substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino,
12	aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylamino, substituted
13	arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl,
14	substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl,
15	substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino,
16	heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl,
17	heteroalkyl, and substituted heteroalkyl;
18	each R ² , R ³ and R ⁵ is a member independently selected from the group consisting of
19	hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, acylamino,
20	substituted acylamino, alkylamino, substituted alkylamino, alkylthio,
21	substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted
22	alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy,
23	substituted arylalkyloxy, amino, aryl, substituted aryl, arylalkyl, substituted
24	arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted
25	arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl,
26	substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl,
27	dialkylamino, substituted dialkylamino, heteroaryloxy, substituted
28	heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted
29	heteroalkyl, hydroxyl, nitro and thio;
30	each R ⁴ is a member independently selected from the group consisting of hydrogen, halo
31	alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino,
32	alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy,
33	substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino,
34	substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl,
35	substituted aryl, arylalkyl, substituted arylalkyl, arylsulfonyl, substituted
36	arylsulfonyl, azido, carboxy, carbamoyl, substituted carbamoyl, carboxyl, cyano,
37	cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl,
38	dialkylamino, substituted dialkylamino, halo, heteroaryloxy, substituted

- heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro and thio;
- and one or more drugs useful in treating vasoconstriction.
 - 1 37. (Previously presented) The method of Claim 1 or 2, wherein the modulator is a compound of a formula that is selected from:

5 109; 110; F₅C

NH₂ 109; 110; F₅C

NH₂ 109; and

- **38.** (Canceled)
- **39.** (Canceled)
- **40.** (Canceled)
- **41.** (Canceled)
- **42.** (Canceled)
- **43.** (Canceled)
- **44.** (Canceled)

Appl. No. 10/621,966 Amendment dated February 2, 2007 Office Action dated December 15, 2006

1 **45.** (Canceled)

1 **46.** (Canceled)

1 **47.** (Canceled)

1 **48.** (Canceled)

1 **49.** (Canceled)

1 **50.** (Canceled)

1 51. (Previously presented) A method of treating vasoconstriction in a patient comprising:
2 administering to the patient a therapeutically effective amount of a modulator of an Edg-1
3 receptor wherein the modulator is a compound of Formula (Ib) is:

$$(R^4)_n$$

$$N$$

$$N$$

$$R^2$$

$$OH$$

$$R^{11}$$

$$O$$

or a pharmaceutically acceptable solvate or hydrate thereof, wherein

n is a member selected from the integers 0 to 5;

R¹¹ is an aryl group;

each R² and R⁴ is a member independently selected from the group consisting of
hydrogen, halo, alkyl, substituted alkyl, acyl, substituted acyl, acylamino,
substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted
alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl,

alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted

4

5

6

- arylalkyloxy, amino, aryl, substituted aryl, arylallcyl, substituted arylalkyl,
 arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy,
 carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl,
 cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted
 dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted
 heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro and thio.
 - 1 **52.** (Previously presented) The method of claim **51**, wherein said aryl group in R¹¹ is a heteroaryl group.
 - 1 53. (Previously presented) The method of claim 52, wherein said compound has the formula:

$$\begin{array}{c|c}
(R^4)_n \\
\hline
\end{array}$$

$$\begin{array}{c|c}
R^2 \\
OH \\
\end{array}$$

$$\begin{array}{c|c}
N \\
\end{array}$$

- 1 54. (Previously presented) The method of claim 53, wherein R² is a substituted alkyl group.
- 1 **55.** (Previously presented) The method of claim **54**, wherein R² is said substituted alkyl group is -CF₃.
- 1 **56.** (Previously presented) The method of claim **55**, wherein n is 1.
- 1 57. (Previously presented) The method of claim 56, wherein R⁴ is a halo group.
- 1 58. (Previously presented) The method of claim 57, wherein said halo group is chlorine.
- 2 **59.** (Previously presented) A method of treating vasoconstriction in a patient comprising:
 3 administering to the patient a therapeutically effective amount of a modulator of an Edg-1
 4 receptor wherein the modulator is a compound of Formula (Ic):

Appl. No. 10/621,966 Amendment dated February 2, 2007 Office Action of December 15, 2006

n is a member selected from the integers 0 to 5;

- each R⁴ is a member independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, alkylarylamino, substituted alkylarylamino, arylalkyloxy, substituted arylalkyloxy, amino, aryl, substituted arylallcyl, substituted arylalkyl, arylamino, substituted arylamino, arylsulfonyl, substituted arylsulfonyl, carboxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroaryloxy, substituted heteroaryloxy, heteroaryl, substituted heteroaryl, heteroalkyl, substituted heteroalkyl, hydroxyl, nitro and thio.
- **60.** (Previously presented) The method of claim **59**, wherein n is 1.
- 1 61. (Previously presented) The method of claim 60, wherein R⁴ is a halo group.
- **62.** (Previously presented) The method of claim **61**, wherein said halo group is chlorine.
- **63.** (Canceled)
- **64.** (Canceled)